

# AMERICAN JOURNAL OF PHARMACY AND THE SCIENCES SUPPORTING PUBLIC HEALTH

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# E D I T O R I A L

On these pages the editor offers his opinions, unshackled by advertising patrons and unrestrained by anything save a sense of the decent and the truthful—the editor, alone, is responsible for their type, their tone and their tenor.

## THE NEW FOOD AND DRUGS ACT

FOR a generation, this Journal has championed the cause of the consumer insofar as it is his right to secure for pay, food that is pure and wholesome and drugs that are true and dependable.

Ever since we were aware of the inadequacy of the 1906 Act to protect the table and the sick room of the American people we have preached for more useful sane legislation in this direction.

And now, after years of carping and quibbling by Congress, the New Deal for food and drug safety is a matter of fact.

This new Federal Food, Drug and Cosmetic Act became law on June 25, 1938, when it was signed by the President. Its general provisions will become effective one year from that date. Certain provisions, however, become effective immediately.

The new law has for its principal differences from the Federal Food and Drugs Act of June 30, 1906, insofar as its *drug* features are concerned:

1. Brings all cosmetics except toilet soaps under control; outlaws cosmetics which may be injurious to health, except poisonous coal-tar hair dyes which bear warning labels; prohibits false or misleading labeling.
2. Brings under control drugs used in the diagnosis of disease and drugs intended to affect the structure or any function of the body.
3. Brings therapeutic devices under control, and subjects them to the same general requirements as are set up for drugs.
4. Prohibits traffic in drugs and devices which are dangerous to health under the conditions of use prescribed in the labeling.
5. Prohibits traffic in new drugs unless such drugs have been adequately tested to show that they are safe for use under the conditions of use prescribed in their labeling; authorizes exemption from this re-

quirement of drugs intended solely for investigational use by qualified scientific experts.

6. Makes the Homeopathic Pharmacopœia of the United States the legal standard for homeopathic drugs.

7. Requires labels of official drugs—*i. e.*, drugs recognized in the U. S. Pharmacopœia, National Formulary or Homeopathic Pharmacopœia of the United States—to reveal any differences of strength, quality or purity from the official standards. (The old law requires merely that the label bear a true statement of the strength, quality and purity of the drug, without showing the difference from the official standard.)

8. Requires drugs intended for use by man to bear labels warning against habit formation if they contain any of a list of narcotic or hypnotic, habit-forming substances, or any derivative of any such substance which possesses the same properties.

9. Requires the labeling of drugs and devices to bear adequate directions for use, but authorizes regulations exempting drugs and devices from this requirement where it is not necessary for the protection of the public health.

10. Requires the labeling of drugs and devices to bear warnings against probable misuse which may be dangerous to health.

11. Requires special precautionary labeling for drugs that are liable to deterioration.

12. Does not contain the fraud joker in the old law under which the Government must prove that false claims of curative effect on the labels of patent medicines were made with wilful intent to deceive.

13. Requires official drugs to be packaged and labeled as prescribed by the Pharmacopœias and Formulary.

14. Defines non-official drugs as illegal if the standard of strength differs from the standard claimed. (The old law prohibits only those which *fall below* the strength claimed.)

15. Requires that antiseptics possess germicidal power.

16. Requires the labels of non-official drugs to list the names of the active ingredients, and in addition to show the quantity or proportion of certain specified substances. Authorizes regulations prescribing

ing exemptions from this requirement when compliance is impracticable.

17. Proscribes the use of containers for food, drugs and cosmetics which may render the contents injurious to health.

18. Prohibits traffic in food, drugs and cosmetics which have been prepared or handled under insanitary conditions that may contaminate them with filth or that may render them injurious to health.

19. Forbids the use of uncertified coal-tar colors in food, drugs and cosmetics other than hair dyes.

20. Proscribes slack filling of containers for foods, drugs and cosmetics, and outlaws the use of deceptive containers.

21. Authorizes factory inspection of establishments producing food, drugs, devices and cosmetics for interstate shipment.

22. Requires that part of samples collected by the Government for analysis be given to the manufacturer on request, but provides exemption from this requirement to the extent necessary for proper administration of the Act.

23. Authorizes the Government to charge fees for the certification of coal-tar colors in amounts necessary to defray the expenses of the service.

24. Limits seizure for misbranding to a single interstate shipment of the product unless the misbranding has been the subject of a prior court decision in favor of the Government, or unless the misbranded article is dangerous to health, or its labeling is fraudulent or would be in a material respect misleading to the injury or damage of the purchaser or consumer. Authorizes consolidation of multiple seizure cases (seizures of two or more interstate shipments of identical goods from the same shipper) for trial in a single jurisdiction. Also authorizes such consolidated cases, as well as cases involving seizure of a single interstate shipment for misbranding, to be removed for trial to any district agreed upon by stipulation between the Government and the shipper or owner of the seized goods. In case of failure to reach such an agreement, the shipper or owner of the goods may apply to the court in which the seizure was made, and the court is required, unless good cause to the contrary is shown, to specify a district of reasonable proximity to the applicant's principal place of business in which the case



will be tried. (The old law places no limitation on the number of shipments of illegal goods which may be seized; contains no provision for change of venue for trial. Seizure cases are tried in the district in which seizure occurs, which ordinarily is the district to which the goods have been shipped for sale and consumption.)

25. Provides for a judicial review in the United States Circuit Court of Appeals to determine the validity of certain regulations. This form of review is an addition to and not in substitution for established forms of review through equity proceedings and proceedings under the Declaratory Judgment Act.

Immediately upon approval of the Act by the President the following provisions became effective:

The prohibition against drugs which are dangerous to health when used in the dosage, or with the frequency or duration prescribed, recommended or suggested in the labeling.

The prohibition against the introduction of new drugs before an application for such introduction becomes effective.

The prohibition against cosmetics which may be injurious to users under the conditions of use prescribed in the labeling or under such conditions as are customary or usual. However, poisonous coal-tar hair dyes which would be exempted under the proviso of this requirement if they bore the warning label prescribed by the statute will not be subject to action by reason of their failure to bear the prescribed warning until ninety days after the date of approval.

All in all, with the expressed hope that the Government will rationally lubricate this law into effective operation, it must be conceded that since the safety of the people is higher than politics, this law was needed far more than some other New Deal legislation recently enacted.

IVOR GRIFFITH.

## ORIGINAL ARTICLE

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### MECHANISM OF ACTION OF APHRODISIAC AND OTHER IRRITANT DRUGS

#### I. PHYSIOLOGICAL EVALUATION OF YOHIMBINE, CANTHARIDIN, CAPSAICIN AND PIPERINE ON DAPHNIA MAGNA\*

By Arno Viehoveer and Isadore Cohen\*\*

(Philadelphia College of Pharmacy and Science)

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\*Presented at the joint session of Medical Sciences of the American Association for the Advancement of Science, Indianapolis, December 27, 1937.

\*\*From the Gross Laboratory for Biological and Biochemical Research.

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## I. INTRODUCTION

With sex playing such an important role in human activity, it is not surprising that from earliest times attention has been directed to increasing the sexual capacity or stimulating sexual sluggishness in both man and beast. The use of aphrodisiacs is a common practice in animal husbandry and breeding.

Although innumerable drugs and dietetic practices have been advocated, cantharidin and yohimbine have received by far the greatest recommendation and use. However, their indiscriminate and often unwarranted use has produced severe toxic effects thus revealing the unsolved problem of their safe application. Obviously there remains the need for the selection and evaluation of an efficient but safe aphrodisiac. We have, therefore, undertaken the study of certain aphrodisiac drugs or substances. In these initial studies, *Daphnia magna*, the transparent crustacean, was selected as a test animal since it had previously shown its merit as a biological reagent in both the specific action and associated effects of drugs (especially narcotics, laxative substances, and potent poisons, etc.).

The substances tested were yohimbine, cantharidin, capsaicin and piperine, and their action compared upon *Daphnia*.

## II. CULTURE AND DIFFERENTIATION OF FEMALE AND MALE DAPHNIA

The propagation of *Daphnia magna* has been reported by Viehovever (7), and further methods of standardization by Viehovever and Cohen (10). Bovung (dried, shredded cow manure), Wizard sheep manure (dried, shredded) and Cellu soybean flour with urea added were used as the basic components of culture media.

The manure media are made up per gallon by first boiling two grams of Bovung or Wizard sheep manure in 50 cc. water and then adding this concentrate to the remainder of the water containing a piece of marble. After fermentation and inoculation of fodder organisms from a successful culture, the media are ready for use after three days. Boiling the manure prevents the development of parasitic flat worms whose eggs might be present in the manure.

The soybean medium is made by adding 500 mg. of Cellu and 100 mg. of urea to a gallon of well aerated, dechlorinated tap water containing a piece of marble. This culture medium can be used on the

day following inoculation with fodder organisms from a successful soybean flour culture.

In order to obtain animals of the same age, gravid females were isolated in one ounce bottles and checked daily. Those which had released young were transferred to a new bottle while the young were all placed together in a gallon jar, half filled with culture media and containing a piece of marble.

While attempts were made to maintain the temperature at 70 degrees F. during cultural and experimental conditions, a variation of  $\pm 4$  degrees F. was recorded between some experiments. At 70 degrees F. the reproductive cycle of daphnia is completed in ten days. The young are products of diploid parthenogenesis and are genetical duplicates of the mother. Having bred this strain of *Daphnia magna* in the laboratory for over ten years, there is no question as to their genetical uniformity.

Under optimum nutritive conditions the number of males born is very scant. However, in starved, stagnant, or crowded cultures, there is an appreciable production of males. Their presence in mass culture can readily be detected by the unexperienced observer by the formation of epiphibia in the females. Epiphibia are black saddle-like structures which occupy the entire brood sac. Usually they are the results of fertilization of the female by the male, and contain two partially developed embryos. To the experienced observer, the males are readily differentiated morphologically from the females in shape, presence of two copulatory hooks and of bristles on the anterior ventral portion of the shell. The presence of a prominent penis extending from the cleansing hook is another distinguishing feature, which is, of course, of particular interest in this study. Moreover, the male is narrower and the absence of a brood sac confers upon it a streamlined appearance as contrasted with the female. The males swim not only more erect but faster.

The penis is a paired structure, consisting of two projections (papillae) with spiny processes which are of apparent aid in the copulatory process.

The testes lie paired on the sides of the digestive tract and connect with the penis, which is located posterior to the cleansing hooks. The testes are hollow tubes in which spermatogenesis without seriation occurs along its entire length. The cells are very small and the meiotic

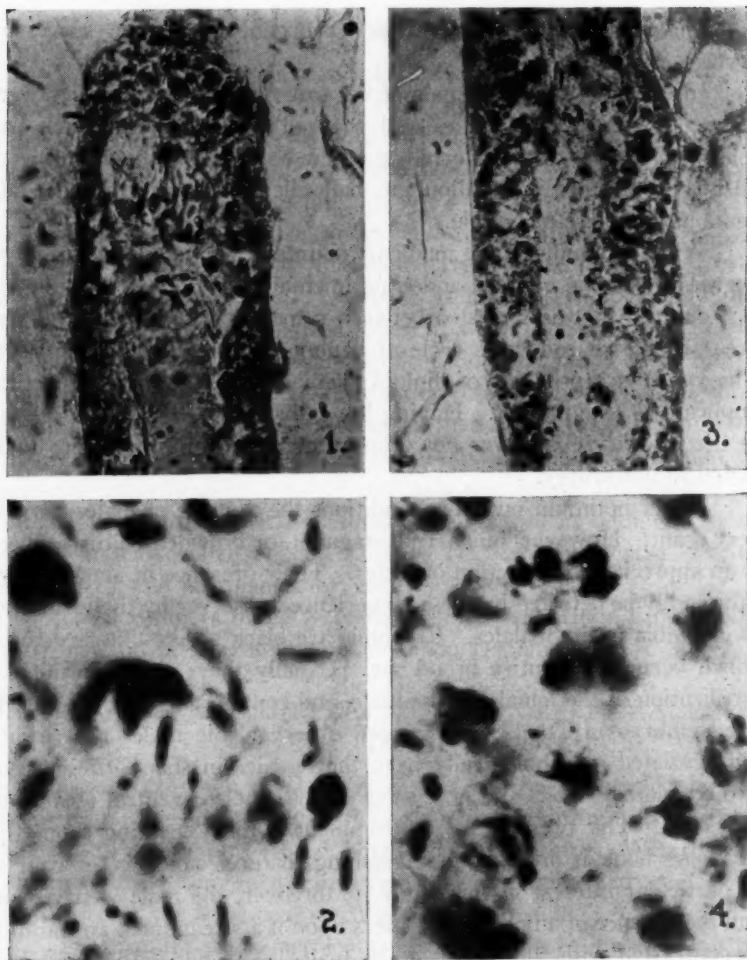


Fig. 1. Median section through upper portion of testis showing sperm lying in the lumen. 660 X

Fig. 2. Enlargement from same section showing shape of sperm lying in lumen. Approximately 2500 X

Fig. 3. Median section through central portion of testis of same daphnia. Note metaphase stages in upper right-hand side. 660 X

Fig. 4. Enlargement to show more clearly the metaphase spindles. Section different from Fig. 3. Approximately 2500 X

Material fixed in Bouin's fluid. Dehydrated in 1) n-butyl alcohol saturated with water, 2) full strength n-butyl alcohol, and infiltrated with paraffin. Stained with crystal-violet-iodine. Zeiss HI 100 oil immersion objective, Leitz 6.6 ocular, Leitz Mikam used with drawtube of microscope extended to 160 mm.



figures accordingly. The chromosomes are minute and cannot be counted with any degree of accuracy. The sperm lie in the lumen of the testis and are large in comparison to the diameter of the meiocytes. The sperm are about 10 micra long and taper at both ends (Fig. 1). They are non-flagellate—a characteristic of crustacean sperm—but their shape is a marked departure from the pelagic crustacea whose sperm are amoeboid.

The testes are surrounded by narrow flat bands of striped muscle which are inserted in the walls of the intestine. In the lower abdominal portions there is an elaborate criss-cross pattern of striped musculature. The antagonistic contractions of these muscles cause a decrease in the size of the lumen of the testes and may thus cause the ejaculation of sperm.

### III. EFFECT OF YOHIMBINE ON DAPHNIA

#### A. GENERAL DATA.

Yohimbine is the alkaloid first isolated in 1896 by Spiegel (6) from the bark of a tropical African tree (*Corynanthe Yohimbe* Schumann), distantly related to the coffee tree. The commercial bark contains over 6 per cent. total alkaloids inclusive of over 1 per cent. yohimbine.

#### *Physical Properties*

Yohimbine forms white needles which become yellowish when in contact with light and air, melting at 247-248 degrees C. The base is dextrorotatory ( $\alpha$ )<sub>D</sub> + 50.9 degrees C. in alcohol, almost insoluble in water, very difficultly soluble in benzene and petroleum ether, readily soluble in ethyl ether, and chloroform. The base is difficultly soluble even in boiling water but is more readily soluble in hot alcohol. The hydrochloride forms a white, bitter, crystalline substance turning yellowish, and then changing to brown at about 245 degrees C., melting at 295-300 degrees C. It is readily soluble in water.

#### *Chemical Properties*

According to most recent information, yohimbine has the formula  $C_{21}H_{26}O_3N_2$ , mol. wt. 354.2, and is believed by some to be identical with quebrachine, the alkaloid found in the white Argentine quebracho bark derived from *Aspidosperma Quebracho blanco* Schlecht. It is

stereoisomeric with the similarly acting corynanthine, the alkaloid from *Pseudo-cinchona africana*. Yohimbine gives strong precipitates with the usual alkaloidal reagents.

#### *Physiological Properties*

Yohimbine is reported to act upon local administration as an anesthetic and vasodilator. On the isolated frog and cat heart it was temporarily stimulating then depressing.

Administered internally, even in smallest amounts, yohimbine is believed to increase the excitability of the breathing center and, in lethal doses, to cause respiratory paralysis first and then paralysis of the heart through injury of the cardiac muscle. It is accumulated in the organism.

According to Sollman (5) yohimbine dilates the vessels of the skin and lowers the blood pressure. It also contracts the spleen, kidneys and intestines. There is an increase in the flow of blood to the cavernous erectile tissues of the penis; an increase of the reflex excitability facilitates erection and produces the effect of sexual stimulation. Yohimbine has been first used for this reason by the natives in tropical West Africa in depressed sex function, due, perhaps, to the extreme hot temperatures (2).

Fatal poisoning of man caused by yohimbine has not been reported. The identity of yohimbine with quebrachine has been questioned because of certain physiological differences observed by Filippi (1).

### B. EXPERIMENTAL DATA

#### *Derangement of the Swimming Mechanism of Daphnia*

Under normal conditions of swimming, the antennæ of the daphnia execute a three-quarter sweep with but a slight angle of divergence outward from the longitudinal axis of the body. Even stroking of the antennæ, usually not more than three beats and followed by a period of rest in which the animal glides a short distance through the medium or momentarily stops, is transformed into a thrusting motion of the entire animal under the influence of yohimbine hydrochloride in the various concentrations tested: 0.2 per cent., 0.1 per cent., 0.05 per cent., 0.025 per cent. The antennæ now execute a full sidewise sweep perpendicular to the longitudinal axis of the body and the animals swim more erect. Moreover, the daphnia seem to have difficulty in swimming to the surface after ten minutes in yohimbine solution.

The normal three beat-rest rhythm becomes a rapid repetition of the three beat rhythm with almost imperceptible rest up to five or six times followed by an exceedingly long rest period, during which the daphnia may fall to the bottom or turn over on their backs, recover and then repeat this peculiar swimming rhythm. The increase of the frequency of the swimming beats of the antennæ here is not considered to be a convulsion but more in the nature of a compensation behavior. From studies of animals in hanging drops, we find that there is a precipitate decrease in the heart beat and respiration. This relationship will be discussed later in greater detail.

An additional change in the swimming mechanism is introduced by the action of yohimbine upon the eye and eye-muscles. The animals swim aimlessly in large spirals and do not avoid colliding among themselves. The cyclopean eye twists markedly under the action of yohimbine and, in addition, the facets appear to bulge out, some more than others. This effect is fixed in the nervous system, for after a day's washing out in culture water, the eye still shows marked torsional movements, while the other activities of the animal return to normalcy except for a slight residual depression in the heart beat rate. The stroking of the antennæ is normal, respiratory movements are fast, and the release of the embryos is not hindered.

When the animals are exhausted in the yohimbine solutions they sink to the bottom of the container with antennæ outstretched and lie on their sides or backs for well over a minute.

*Toxicity of the Solutions as Evidenced by the Inability of the Daphnia to Ascend*

The swimming mechanism of the daphnia is so important that any impairment to it may be considered generally as an important toxic symptom of an active chemical agent that is being tested.

Museum jars, measuring  $14\frac{1}{2} \times 9\frac{1}{2} \times 1\frac{1}{2}$  cm., filled to 8.4 cm. in height with the various concentrations of yohimbine hydrochloride under test, were as satisfactory as when used for a similar purpose in the study of strychnine action (10). When supported on wooden blocks with the proper size groove, the jars could be readily handled. Fifteen gravid female daphnia of approximately eighteen days in age, all of excellent vitality, were placed in the following concentrations of yohimbine: 0.2 per cent., 0.1 per cent., 0.05 per cent., 0.025 per cent. The detailed description of the movements of animals to various

heights in the test solutions, the museum jars being marked in quarters of 2.1 cm., adds little in appreciating the downward tendency of the animals due to exhaustion. It should be remembered that as soon as an animal may recover sufficiently to leave the lowest quarter, another animal will take its place. Hence, while the number of animals down remain constant, the animals themselves are changing in position. This, of course, is of little importance since it does not impair the observation that the tendency of animals is towards the lowest quarter.

#### NUMBER OF DAPHNIA IN LOWEST QUARTER

##### CONCENTRATIONS OF YOHIMBINE HCl

Time		0.2%	0.1%	0.05%	0.025%	Control
After	7 min.	12	12	9	5	3
"	10 min.	14	13	10	5	4
"	18 min.	12	15	14	9	3
"	118 min.	13	14	15	15	4

After three hours three animals from each concentration were taken out and placed into culture water (soybean-urea) and records taken of the heart beat and other details as recorded below.

It may be stated here that the animals in the two lower concentrations were more active in their swimming movements than those daphnia in the two higher concentrations of yohimbine tested. The heart beat of an animal taken at random from 0.2 per cent. yohimbine after two hours was 84 per minute, while the heart beat of one taken from the 0.05 per cent. yohimbine was 192 per minute. The respiratory movements of the latter animal were faster than in the former. The degree of debility here may well be directly proportional to the degree of the depression of the heart and respiratory movements. The heart beat of a daphnia taken at random respectively from each of the concentrations of yohimbine after two and one-third hours was as follows:

0.2%	140 min.	80/min.	0.05%	151 min.	164/min.
0.1%	145 min.	120/min.	0.025%	158 min.	166/min.

Three hours after the start of the experiment, three animals were taken out of each concentration of yohimbine and placed into culture water. Then the heart beats of single animals, taken at random, from those washing out were:

0.2%	38 min. washing out	108/min.	0.05%	43 min. washing out	186/min.
0.1%	42 min. washing out	150/min.	0.025%	46 min. washing out	224/min.

This experiment in recoverability was allowed to continue until the following day. Meanwhile, release of the young had taken place in one of the animals being washed out in the culture medium. The rate of heart beat of the washed out animals after nineteen and one-half to twenty and one-half hours was determined.

Normal heart beat 280 per minute at 70 degrees F.

Animals from 0.2% yohimbine: 202, 147, 179 = 176 ave./min.

Animals from 0.1% yohimbine: 242, 185, 182 = 203 ave./min.

Animals from 0.05% yohimbine: 261, 328\*, 290 = 275 ave./min.

Animals from 0.025% yohimbine: 282, 252, 252 = 262 ave./min.

Controls: 323, 339, 324 = 328 ave./min.

The temperature was 74 degrees F. during the period of this experiment, and this factor is, no doubt, responsible for the higher than average heart beat rate recorded in the controls.

#### *Accumulative Action of Yohimbine*

At the end of twenty hours the animals in the 0.2 per cent. and 0.1 per cent. concentrations were dead. In the lower concentrations, 0.05 per cent. and 0.025 per cent., the animals were still alive; some were unable to swim upward for more than a few body lengths, while the majority were at the bottom in a quiescent state. At the end of twenty-four hours a detailed inspection of each animal in the latter concentrations was made.

In 0.05 per cent. yohimbine hydrochloride dissolved in culture water, advanced debility was the general finding: Coma and post coma and one death, the terminology as proposed by us in a previous publication (10), would serve as a concise description here. Two daphnia, in post coma, had no heart beat but did have a slight torsional movement of the eye and showed slight twitchings in the lower abdomen, respiratory organs and antennæ. The main portion of the intestinal tract was paralyzed. Five animals could be grouped in the stage of coma. Pronounced torsion of eye, sporadic respiratory twitching of antennæ of adult and of embryos in brood sac, slight movement in the lower abdomen in the region of the cleansing hooks but paralysis of the main portion of the digestive tract were the obvious symptoms in this group. The rate of heart beat per minute in the different animals are given: 4, 4, 4, 9 and 10. One animal was rather active as compared

\*The release of young from this animal places it into a different physiological class. Its heart beat is not computed in the average.

to the rest, in that it would sporadically swim about an inch before resting. The heart beat was determined as 63 per minute, respiratory movements at 106 per minute, marked torsion of the eye, intestine not paralyzed. Respiratory movements were very irregular. The extreme case in this group was the one dead animal.

In 0.025 per cent. yohimbine hydrochloride, the daphnia were more active and a microscopic inspection of each animal revealed that the internal mechanisms were functioning on a higher level than in the previous class. All showed marked torsional movements of the eye, depressed but active respiratory movements (140 per minute), no paralysis in the intestinal tract, the antennae of the embryos in the brood sac moved actively, and the heart beat was on the whole significantly higher than found in the first class. One animal was dead, one had the lowest heart beat of 4 per minute and the others had the following rate: 40, 60, 72, 72, 100, 102, 102, 104 per minute. One male, which had been placed into this group three hours after the start of the experiment on the previous day, had a heart beat of 130 per minute.

The data of the effect of yohimbine hydrochloride at various concentrations show that over periods of several hours, the differences in concentration and speed of action can be seen and estimated on the basis of degree of debility of the test animals.

#### *Effect of Yohimbine Hydrochloride Upon Evacuation*

The initial effects of yohimbine hydrochloride in concentrations of 0.2 per cent., 0.1 per cent., 0.05 per cent., and 0.025 per cent. are to increase, perhaps through its bitterness, the peristaltic action in the stomach. Evacuation up to 25 per cent. might take place, rarely more with animals older than ten days. The effect here is suggestive of irritation. In more dilute concentrations, 0.01 per cent. and 0.005 per cent. of yohimbine hydrochloride, most of the animals from seven to ten days old evacuate fully within an hour but under conditions non-comparable with the tentative assay method of laxative evaluation submitted to the collaborators of the Association of Official Agricultural Chemists (11). However, the heart beat is markedly depressed—a serious objection to its possible use as a laxative. Old daphnia (thirty days) heavily laden with embryos, observed in V-tubes containing about 1 cc. of .0033 per cent. yohimbine did not show evacuation over twenty hours. The problem of laxative action is a complex one, and the object of considerable amount of inquiry by one of us (8, 11). The



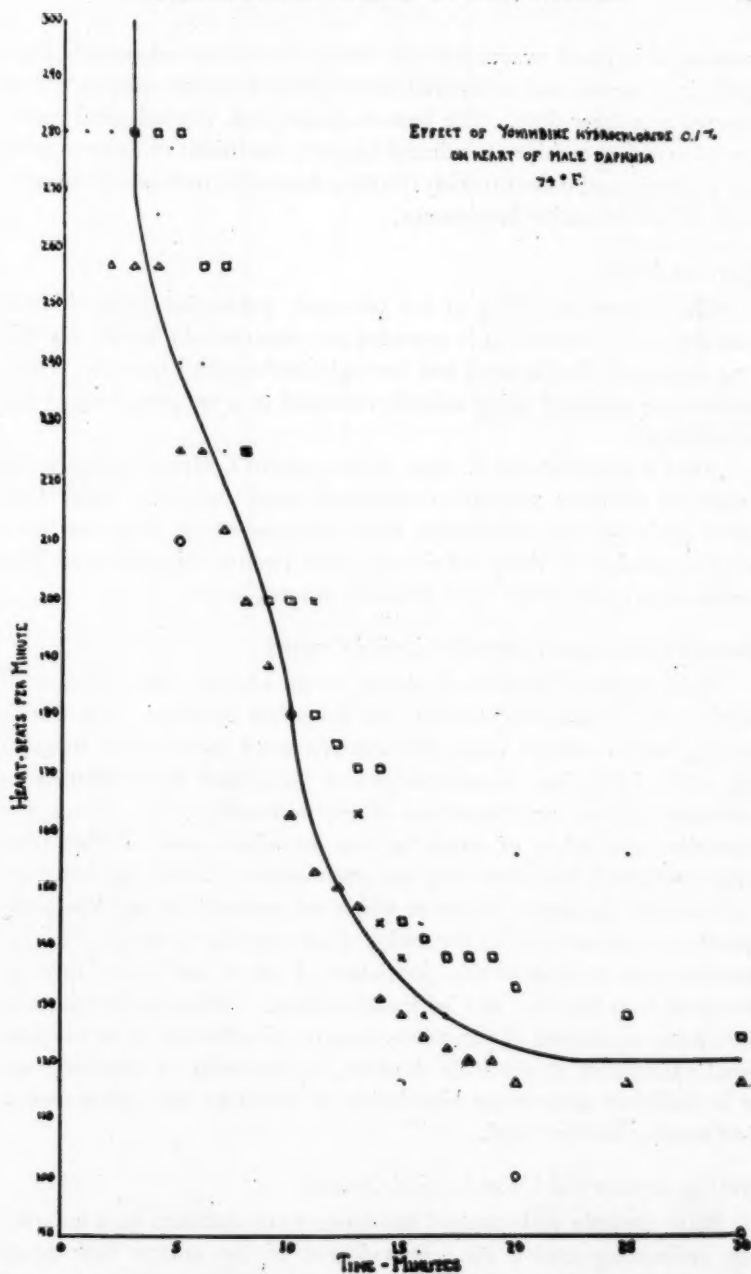


Fig. 5. Cardiac depressant action of 0.1% yohimbine hydrochloride upon 5 nine-day old female daphnia.

question of induced evacuation can hardly be treated adequately here. Work in progress and additional investigations on the subject will be reported at a later date. The factors of age, sex, physiological condition ( $\pm$  ovaries, embryos), cultural history, conditions of experimentation (volume and concentration of test substances, method of observation), all are of major importance.

#### *Effect on Heart*

The depressant effect of 0.1 per cent. yohimbine hydrochloride upon the rate of heart beat is recorded for nine-day-old female daphnia at 74 degrees F. in Figure 5 and for male daphnia in Figure 6. These results were obtained using animals mounted in a hanging drop of the test solution.

After a latent period of three to five minutes, dependent upon the amount of contents present in intestinal canal and little understood factors in the process of diffusion and resorption of the drug, the heart shows a precipitate drop within the next twenty minutes, and then remains depressed at the same level for several hours.

#### *Effect of Yohimbine Upon the Genital Organs*

Male daphnia were first placed in an alcohol free solution of cascara 1-75 in order to evacuate the intestinal contents. Then after washing out in culture water the animals were mounted on hanging drop slides in various concentrations of yohimbine hydrochloride to determine whether any expulsion of sperm would occur. Hence the precaution was taken of emptying the intestinal canal so that fecal matter would not interfere with the observation. Under the influence of yohimbine, the lower abdomen whips out periodically and the penis appears to respond as if in the midst of an ejaculatory thrust. So far attempts made to observe the ejaculation of sperm and collect them in a hanging drop have not met with any success. While the irritant and aphrodisiac properties of yohimbine may be of sufficient value to cause sexual excitement in the male daphnia, the intensity of reaction may not be sufficient to provoke ejaculation of sperm as seen when croton oil or cantharidin are used.

#### *Effect of Croton Oil Upon Genital Organs*

Male daphnia with cleared intestines were mounted in a hanging drop containing croton oil. Ejaculation of the sperm took place

**COMPARATIVE PHYSIOLOGICAL ACTION**  
**YOHIMBINE HYDROCHLORIDE**

Conc.	Appl. Method	Age, Days	Musc. Syst.	Time	Digestive S.	Time	Respiration	Time	Cardiac S.	Time	Gland. S.	Time	Nervous
0.2%	Hanging Drop	9	Deranged	3-5 Min.	Irritated	3-5 Min.	Depressed	After 3 Min.	Depressed	After 3 Min.	Shrinkage of Liver	24 hrs.	Eye Irr.
0.1%	" "	15-20	"	"	"	"	"	"	" (58% Lowered)	20 Min.	Excites Penis	3-5 Min.	"
.2%	Flat Museum Jars (100 cc.)	"	"	"	"	"	"	"	Depressed	After 3 Min.	"	"	"
.1%		"	"	"	"	"	"	"	"	"	"	"	"
.05%		"	"	"	Incomplete Evacuation	"	"	"	"	"	"	"	"
.025%		"	"	"	"	"	"	"	"	"	"	"	"
.05%	Chamber (10 cc.)	7-9	"	"	Evacuation { 100% (7) 50% (1)	35 Min. 35 Min.	"	"	30% Lowered	60 Min.	—	—	—
.003%	" "	"	"	"	100% (4)	60 Min.	"	"	Depressed	—	—	—	—
.0025%	" "	"	"	"	{ 100% (3) 50% (1)	41 Min. 41 Min.	Slight	"	"	—	—	—	—
1:55,000	Flat Museum Jar	7	"	24 hrs.	None	24 hrs.	None	24 hrs.	30% Lowered	24 hrs.	—	—	—

**CANTHARIDIN**

1:30,000	Flat Museum Jar	Female	—	—	—	—	—	—	—	—	—	—	—
1:30,000	Hanging Drop	Male	—	—	—	—	—	—	—	—	Sperm Ejected	After 3 Min.	—
Suspension	" "	Female	Stopped	25 Min.	Local Swelling	25 Min.	Stopped	25 Min.	{ Normal Stopped	25 Min. 70 Min.	— Sperm Ejected	— After 3 Min.	Paralyze
"	" "	Male	"	"	" "	—	—	—	—	—	—	—	—
1:55,000	Museum Jar	Female (7)	—	—	—	—	—	—	—	—	—	—	—

**CAPSAICIN**

1:30,000	Museum Jar	15-20	{ Normal Weakened	2 hrs. Several	—	—	Depressed	2 hrs.	Depressed	2 hrs.	—	—	Eye Irr.
Suspension	Hanging Drop	Female	—	—	Local Swelling	20 Min.	"	20 Min.	"	20 Min.	—	—	"
"	" "	Male	—	—	—	—	—	—	—	—	Excites Penis	—	Paralyze
1:55,000	Museum Jar	7	—	—	Evacuation 50%	24 hrs.	Fast	24 hrs.	{ 30% Lowered Slight	24 hrs. 48-72	—	—	—

**PIPERINE**

Sat.	Museum Jar	12	{ Slow Swimming	24 hrs.	Evacuation 80-100%	1½ hrs.	—	—	60% Depressed	24 hrs.	—	—	—
Sat.	Hanging Drop	Female (9)	—	—	—	—	—	—	Irreg.	2 hrs.	—	—	—
"	" "	Male (14-15)	—	—	—	—	—	—	60% Lowered	1 hr.	Excites Penis	3-5 Min.	—
1:55,000	Museum Jar	7	—	—	Evacuation 50%	24 hrs.	Depressed	24 hrs.	25% Lowered	24 hrs.	—	—	—

VE PHYSIOLOGICAL ACTION  
MBINE HYDROCHLORIDE

iration	Time	Cardiac S.	Time	Gland. S.	Time	Nervous S.	Time	Toxicity	Time
essed	After 3 Min.	Depressed	After 3 Min.	Shrinkage of Liver	24 hrs.	Eye Irrit.	After 3 Min.	—	—
"	"	" (58% Lowered)	" 20 Min.	Excites Penis	3-5 Min.	"	"	—	—
"	"	Depressed	After 3 Min.	"	"	"	"	Death	Within 24 hrs.
"	"	"	"	"	"	"	"	"	Within 20 hrs.
"	"	"	"	"	"	"	"	{ Advanced Debility 1 Death	"
"	"	"	"	"	"	"	"	{ Debility 1 Death out of 25	"
"	"	30% Lowered	60 Min.	—	—	—	—	—	—
"	"	Depressed	—	—	—	—	—	—	—
ight	"	"	—	—	—	—	—	—	—
one	24 hrs.	30% Lowered	24 hrs.	—	—	—	—	Swimming in Lower 10th Height	Up to 72 hrs and after

CANTHARIDIN

—	—	—	—	—	—	—	—	Death	Within 24 hrs.
—	—	—	—	Sperm Ejected	After 3 Min.	—	—	—	—
opped	25 Min.	{ Normal Stopped	25 Min. 70 Min.	— Sperm Ejected	— After 3 Min	Paralyzed	25 Min.	Death	70 min.
—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	Death	Within 24 hrs.

CAPSAICIN

ressed	2 hrs.	Depressed	2 hrs.	—	—	Eye Irrit.	2-4 Min.	50% Death	20 hrs.
"	20 Min.	"	20 Min.	—	—	"	Up to 1 hr.	Death	3½ hrs.
—	—	—	—	Excites Penis	—	Paralyzed	After 1 hr.	—	—
Fast	24 hrs.	{ 30% Lowered Slight	24 hrs. 48-72	—	—	—	—	{ 1 Death out of 25	24-72 hrs. and after

PIPERINE

—	—	60% Depressed	24 hrs.	—	—	—	—	1 Alive	48 hrs.
—	—	Irreg.	2 hrs.	—	—	—	—	—	—
—	—	60% Lowered	1 hr.	Excites Penis	3-5 Min.	—	—	—	—
ressed	24 hrs.	25% Lowered	24 hrs.	—	—	—	—	1 Death out of 25	24-72 hrs. and after

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General Ledger					
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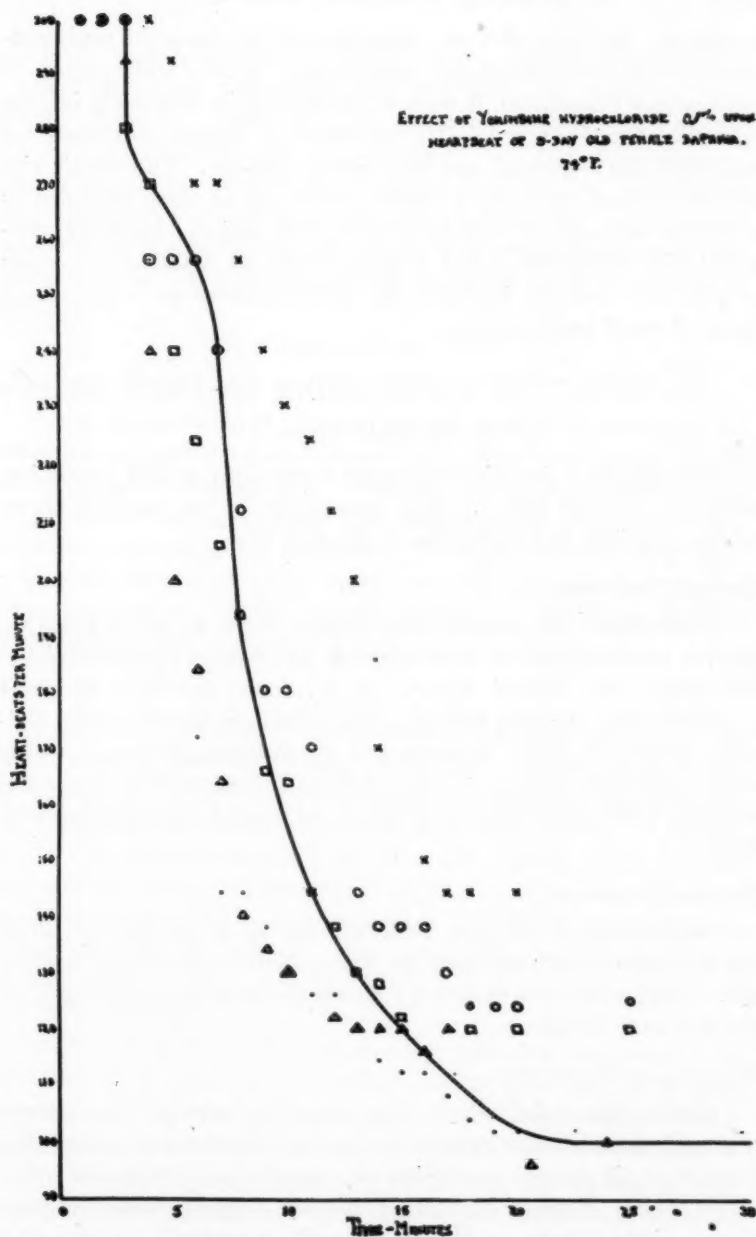


Fig. 6. Cardiac depressant action of 0.1% yohimbine hydrochloride upon 5 male daphnia.

periodically, and even after the exhaustion of the store, the penis continued to execute its ejaculatory movements. Hence, while croton oil does produce ejaculation, it does so because of its extremely irritant and toxic cramping action. The intestines of daphnia so treated are constricted and contorted, and the animals soon die. The drastic violence of reaction obviously precludes croton oil as being classified as an irritant substance of beneficial aphrodisiac action. However, contrasted with cantharidin, which is treated later, the differences in action between them upon the intestinal and genital systems are a question of degree of speed and intensity.

#### IV. EFFECT OF CANTHARIDIN ON DAPHNIA

##### A. GENERAL DATA

Cantharidin is the blistering agent occurring free and in salt formation up to 2 per cent. in about 250 species of the so-called blister beetles, especially in *Cantharides* or Spanish flies.

##### *Physical Properties*

Cantharidin, colorless rhombic leaflets, melts at 218 degrees C., sublimes undecomposed at approximately 120 degrees C. and is volatile with water and alcohol vapor. It is almost insoluble in water (1:30,000 cold, 1:15,000 boiling), little soluble in alcohol, fairly difficultly soluble in ether, benzene and chloroform, and most readily soluble in acetone (1:40). From solutions in concentrated formic and sulphuric acids cantharidin is separated unchanged upon dilution with water.

##### *Chemical Properties*

Cantharidin,  $C_{10}H_{12}O_4$ , mol. wt. 196.09, is an acid anhydride and is changed by alkalis into the water soluble salts of cantharidinic acid. No characteristic chemical tests for the identification of cantharidin appear to be known.

##### *Physiological Properties*

Cantharidin is the irritant, heat producing principle incorporated in special plasters recommended in earache. Cantharidin causes local irritation in all tissues and organs, even small doses irritate the urino-genital system; in larger amounts it causes first inflammations, pustules, blisters of the mouth, esophagus, stomach, intestines, then vomiting

and bloody stools, and, finally, injury to the kidney (albuminuria). In severe poisoning, cantharidin may also affect the central nervous system. There is a disturbance of breathing, fainting, collapse and cramps. Its aphrodisiac action is considered due to the sensory irritation of the mucous membranes in the urogenital tract, accompanied by vasodilation. Cantharidin is carried throughout the organism and is excreted unchanged through the urine. Oils accelerate the poisonous action of cantharidin probably through increased solution and rate of absorption.

#### B. EXPERIMENTAL DATA

##### *High Dilution (1:30,000)*

In the concentration of 1:30,000 in culture water at 70 degrees F., cantharidin does not show any obvious rapid effects upon fifteen female daphnia placed in museum jars. However, this concentration of cantharidin will kill within a twenty-four hour interval. Evidently it is a case of accumulation and of resorption. In males, observed in a hanging drop, ejaculation of sperm occurs with the periodic thrusting of the lower abdomen as in the case of yohimbine. This latter fact has already been reported by one of us (9).

##### *Suspension*

A suspension of cantharidin was made by triturating a few crystals on a watch glass with two drops of acetone. Cantharidin is soluble 1:40 in acetone. The acetone was allowed to evaporate, and then two drops of culture fluid were added and vigorously stirred. A female daphnia, with 100 per cent. filled intestine and without embryos in the brood sac, was placed in a hanging drop of this suspension. Another animal of the same size and physiological condition was placed in a syracuse dish in a few drops of the cantharidin suspension (also a 1:30,000 solution). The syracuse dish was kept covered in order to minimize evaporation.

At the end of twenty-five minutes the heart beat was normal, no evacuation occurred but paralysis of the eye; antennae and respiratory movements were stopped. The lining of the intestinal tract presented a corrugated appearance indicating the extreme intensity of irritation.

At the end of fifty minutes the heart beat and rhythm in both animals were normal, (280-290) in spite of the cessation of all other vital activities. The heart continued to beat normally for ten more minutes and then abruptly became irregular with several triple beats.

The rate dropped rapidly ending finally, at the end of seventy minutes, in death.

Males, which had been previously cleared of their intestinal contents, when mounted in a hanging drop of the suspension of cantharidin reacted with the ejaculation of sperm in the lower concentration. However, death occurred much faster.

## V. EFFECT OF CAPSAICIN ON DAPHNIA

### A. GENERAL DATA

Capsaicin, the pungent principle of capsicums or red pepper pods, occurs in the oil secretion glands of the placentæ. It is also known to occur in certain other varieties such as African or Japanese chillies and cayenne pepper.

#### *Physical Properties*

Capsaicin forms colorless platelets of intensely burning taste, melting at 63-65 degrees C. It is only little soluble in cold water, more soluble in boiling water, and readily soluble in petroleum benzine, alcohol, ether, glacial acetic acid, hot carbon disulphide and fatty oils.

#### *Chemical Properties*

Capsaicin has a weakly acid character and contains a phenol group. Its formula  $C_{18}H_{27}O_3N$ , mol. wt. 307.16, has been determined by Micko (3). According to Nelson (4) it is a condensation product of vanilylamine with dicylenic acid.

It is not precipitated, or only very slightly with the usual reagents which precipitate alkaloids.

#### *Physiological Properties*

The peculiar delectable pungency of the red peppers causes their abundant use as condiments in highly spiced dishes, especially in chile con carne, curries and tabasco sauces, and in beverages as ginger ale. The local irritating effect upon the nasal mucous membranes which causes prolonged sneezing is well known to those who have worked with the pure capsaicin. Of similar common knowledge is the burning sensation of the skin produced by the local application of capsicum plasters. In these plasters oleoresin which contains capsaicin is incorporated.

Capsaicin, and therefore capsicums, powerfully stimulate locally the heat receptors and create the sensation of warmth which increases

to that of severe pain and intolerable burning in concentrated solutions, with practically no erythema nor blistering of membranes nor narcotic effect. When swallowed, capsaicin does not blister the membranes nor produce a narcotic effect. There is little effect upon the capillaries or other blood vessels. However, there is a strongly irritating effect upon the sensory nerve endings.

#### B. EXPERIMENTAL DATA

##### *Effect of Capsaicin in Solution (1:30,000)*

In 1:30,000 concentration in culture water, capsaicin showed little rapid effect upon animals placed in museum jars. At the end of two hours, swimming was apparently normal but the heart beat was noticeably depressed. At the end of twenty hours, there was a 50 per cent. mortality. The animals died on the surface of the solution. This may have been due to the weakening of the power in the stroke of the antennæ and the daphnia were trapped by surface tension. Shaking the jar freed the animals. Those that were dead or could no longer move their antennæ remained at the bottom, but those that could still swim soon became trapped again at the surface film. There was tremor in the eyes of those which were still alive and the heart beat and respiratory movements were much depressed.

##### *Effect of Capsaicin in Suspension*

A suspension of capsaicin was made by triturating a few platelets of capsaicin on a watch glass with a few drops of culture water. A female daphnia, with intestine 100 per cent. filled and without embryos in the brood sac, was placed in a hanging drop of this suspension. Another animal of the same size and condition was placed in a syracuse glass in a few drops of the capsaicin suspension. The syracuse dish was covered to minimize evaporation.

At the end of ten minutes the heart beat began to drop precipitately and by twenty-eight minutes the rate was sixty per minute. The detailed data is as follows:

Normal heart beat 280 per minute at 70 degrees F.

After 10 min.: 232 per minute  
After 11 min.: 180 per minute  
After 12 min.: 150 per minute  
After 13 min.: 150 per minute

After 16 min.: 112 per minute  
After 18 min.: 105 per minute  
After 23 min.: 84 per minute  
After 28 min.: 60 per minute

At the end of twenty minutes the respiratory movements dropped to 180 per minute. Although the intestinal contents were broken up and the intestine took on a corrugated appearance, evacuation was slight.

The effect of capsaicin upon the eye was most spectacular. The eye turned first in one direction with as much torque as possible and then immediately turned fully in the other direction. This effect lasted approximately for an hour, after which time paralysis or exhaustion brought this activity to a close.

With the further elapse of time the debility of the animal increased, for after forty-five minutes the heart ceased beating regularly. The heart, greatly dilated, stopped for well over a minute (72-80 seconds) and then recovered for 20-30 slow beats (1 per second). At this point respiratory movements had dropped to 30-40 per minute. The antennæ did not beat as frequently as previously and the animal lapsed into coma, post coma, and finally death after three and one-half hours.

During the duration of the experiment, the animals, evacuated but slightly (5-10 per cent. of the entire gut). The most striking effect was the breaking up of the contents into small lumps and segments. A prominent stricture at the beginning of the hind gut was observed about three-quarters of an hour after the start of the experiment.

Capsaicin resembles yohimbine more in its effect upon the heart and eye than cantharidin. Upon the digestive tract the effect of capsaicin resembles cantharidin more than yohimbine. The thrusting motion of the lower abdomen where the penis projects was studied upon previously evacuated males in the same type of capsaicin suspension, but no ejaculation of sperm was observed.

## VI. EFFECT OF PIPERINE ON DAPHNIA

### A. GENERAL DATA

Piperine occurs up to 5.7 per cent. in the ethereal oil of the berries of black pepper which owes its pungency to this principle. White pepper is the dried mature berry of the same plant from which one or more outer layers have been removed after maturity. Black and white pepper are derived from *Piper nigrum* (family Piperaceæ) and should not be confused with red pepper which is derived from *Capsicum* (family Solanaceæ) and whose principle is capsaicin.



*Physical Properties*

Piperine forms colorless, shining, monoclinic needles from alcohol, which melt at 128-129.5 degrees C., have a density of 1.193 and are optically inactive. Piperine is very slightly soluble in cold water, soluble in chloroform, ether and benzene, and is soluble up to 6.7 per cent. in alcohol at 23 degrees C.

*Chemical Properties*

Piperine, 3-piperylpiperidine, has the formula  $C_{17}H_{19}O_2N$ , mol. wt. 285.16, and is a very weak base or alkaloid. It is readily characterized by the blood-red color obtained when treated with concentrated sulphuric acid, and forms with concentrated nitric acid an orange-red resin.

*Physiological Properties*

The spice value of black peppers and white peppers is long known and they are used daily in many homes and restaurants. In medieval times the liberal admixture of pepper to dishes prepared from meat, too well hung, was a common practice in order to disguise the tainted taste. The action of pepper or piperine as a local excitant has long been known and satisfactorily employed. Piperine is said to lower slightly the temperature in man and, like capsaicin and gingerol (active principle of ginger), it is one of those substances causing selective stimulation of the heat receptors. The use of piperine in higher concentrations produces a strong sensation of heat which increases to a sensation of burning and of severe pain without inflammation.

**B. EXPERIMENTAL DATA**

Twelve twelve-day-old daphnia were placed in a museum jar three-quarters filled with saturated piperine. A control was run.

Evacuation from 80 to 100 per cent. occurred within the first one and one-half hours, although there was a definite longitudinal contraction of the midgut. Twenty-four hours later all the animals were alive but swam very sluggishly. Their heart beat ranged from 95 to 106 per minute. Forty-four hours later there was only one alive.

Two male daphnia (14 and 15 days old), placed in a hanging drop of saturated piperine, showed a depression of their rate of heart beat as did five female daphnia (9 days old). Continued excitatory movements of the sex organ and initial quiver in the grasping hooks

are quite pronounced in male daphnia. Their intestines had been cleared previously, but ejaculation of sperm could not be seen. As in the case of yohimbine and capsaicin, the intensity of piperine action at such concentration may not be sufficient to provoke ejaculation.

#### DEPRESSION OF HEART BEAT RATE BY PIPERINE

Start: 320 per minute		Start: 320 per minute	
<i>Male</i>		<i>Male</i>	
After	After	After	After
9 min.: 240/min.	44 min.: 138/min.	9 min.: 320/min.	29 min.: 171/min.
13 min.: 240/min.	50 min.: 132/min.	10 min.: 288/min.	30 min.: 150/min.
20 min.: 200/min.	55 min.: 130/min.	12 min.: 277/min.	42 min.: 109/min.
26 min.: 189/min.	64 min.: 129/min.	15 min.: 267/min.	48 min.: 95/min.
31 min.: 170/min.	73 min.: 130/min.	20 min.: 218/min.	51 min.: 90/min.
37 min.: 157/min.		23 min.: 212/min.	56 min.: 90/min.
		27 min.: 200/min.	60 min.: 90/min.
		28 min.: 185/min.	

Start: 300 per minute	
<i>Female</i>	
After	After
5 min.: 200/min.	68 min.: 106/min.
13 min.: 134/min.	120 min.: irreg.
18 min.: 123/min.	

#### VII. COMPARATIVE TOXICITY OF YOHIMBINE, CANTHARIDIN, CAPSAICIN and PIPERINE

Twenty-five seven-day old daphnia were placed respectively in each 100 cc. of 1:55,000 solutions in culture water of 1) yohimbine, 2) cantharidin, 3) capsaicin, and 4) piperine in the museum jars, three-quarters filled. A control was also run.

*Twenty-four Hours Later the Following Results Were Obtained*

Control: all alive.

1) Cantharidin: all dead.

2) Yohimbine: all alive but swimming in the lowest tenth of the jar. Average heart beat of six animals taken at random (195, 180, 175, 180, 184, 189) = 184 per minute. The respiratory movements

were fast, the intestines 100 per cent. filled and there was no noticeable shrinkage of the liver.

3) Capsaicin: one dead. Average heart beat of seven animals selected at random (171, 180, 167, 164, 162, 180, 184) = 172 per minute. Respiratory movements were fast, intestines 50 per cent. filled, and there was no marked shrinkage in the liver.

4) Piperine: one dead. Average heart beat of 6 animals taken at random (240, 225, 225, 225, 218, 225) = 226 per minute. Respiratory movements were moderate, intestine 50 per cent. filled, and there was no shrinkage of liver.

*Forty-eight Hours Later the Following Results Were Recorded*

Control: all alive.

2) Yohimbine: most animals in lower tenth, few able to swim to surface. Average heart beat for six animals taken at random = 213 per minute; all alive.

3) Capsaicin: animals apparently normal, heart beat ranging from 270 to 280 per minute; all alive.

4) Piperine: same appearance as for capsaicin, but heart beat from 240 to 270 per minute; all alive.

*Seventy-two Hours Later the Following Results Were Recorded*

Control: all alive.

2) Yohimbine: still at bottom, heart beat ranging from 180 to 225 per minute; all alive.

3, 4) Capsaicin and Piperine: appear the same as on previous day with heart beat slightly depressed; all alive.

It is evident that the order of decreasing toxicity of tested substances is cantharidin, yohimbine, and finally capsaicin and piperine of approximately equal toxicity at 1:55,000 concentration in culture water.

## VIII. TABULATED COMPARATIVE PHYSIOLOGY OF TEST SUBSTANCES

A survey of the specific effects on the various organs is given on the chart. The inflammatory, specific and highly toxic effect of cantharidin in contrast to the potent but milder effect of yohimbine, capsaicin and piperine is obvious from statements here recorded.

The results are not included of the violent and almost spontaneous evacuation obtained with croton oil, of which a minute amount was introduced into the culture water. The study of *Muira puama* and ginseng root and their active ingredients as possible aphrodisiacs might be undertaken in a similar comparative way.

We wish to acknowledge the cooperation of Mr. Linwood F. Tice in supplying us with capsaicin used in this investigation.

### IX. SUMMARY AND CONCLUSIONS

1. A physiological method has been devised for the study of the mechanism of action of sexual stimulants (aphrodisiacs) and their evaluation using *Daphnia magna*, the transparent crustacean, as a test animal.
2. Both the specific action and the associated physiological effects of the following four substances were recorded: yohimbine (HCl salt), derived from the bark of a tropical African tree distantly related to the coffee tree; cantharidin, an ovarian and tissue product of the blister beetles; capsaicin, the pungent principle of red peppers; and piperine, that of black pepper.
3. All four substances cause pronounced and continued excitatory movements of the male genital organ. Actual ejaculation of the sperm was observed with the use of cantharidin.
4. In varying concentrations the order of increasing lethal toxicity was found to be piperine, yohimbine, capsaicin and cantharidin.
5. These agents in high concentration also produce irregular clumping and stasis of the intestinal contents as a result of the progressive and prominent swellings in the lining of the intestinal canal. In low concentration, 0.0033-0.0025 per cent. yohimbine causes evacuation in young daphnia (7 to 9 days old); while capsaicin and cantharidin, both 1:30,000, show as a rule no indication of valuable laxative properties, their local irritant action apparently prevailing.
6. Yohimbine, capsaicin and piperine in varying concentration depress progressively both the heart, producing dilation, and the respiratory movements. Cantharidin in suspension stops first all vital activity except that of the heart, which then shortly collapses.
7. Gravid females exposed to 0.1-0.025 per cent. yohimbine for three hours can be recovered by returning them to culture media

although there remains even after twenty-four hours a partial depression of the heart beat. Normal life activity, including the release of several broods of young, was observed subsequently.

8. Yohimbine and capsaicin in varying concentrations produce an exaggerated torsion of the muscles controlling the movements of the eye. Paralysis of these movements occurred after one hour in a suspension of capsaicin.
9. The alteration in the normal swimming of animals under the influence of yohimbine (0.2-0.025 per cent.) and capsaicin (suspension) is caused by the incoordination of antennal movements, and, possibly in part, by the derangement in the optical system.
10. The derangement of the swimming mechanism correlated with the internal disturbances can obviously be used as criteria in establishing the toxicity of test substances.
11. These results with *Daphnia magna* furnish additional evidence that there are no sharply demarcated physiological differences between invertebrates and vertebrates. Certain specific and associated effects coincide with previous findings on vertebrates.
12. The value of *Daphnia magna* as a biological reagent is further demonstrated by the unmistakable and consistent responses of the anatomical and physiological systems to these additional test substances.

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## ABSTRACTS FROM AND REVIEWS OF THE LITERATURE OF THE SCIENCES SUPPORTING PUBLIC HEALTH

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Biochemistry, Nutrition, etc. . . . .	Arno Viehoveer, Ph. D.
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Chemistry . . . . .	Arthur Osol, Ph. D.
Pharmacy . . . . .	E. Fullerton Cook, Ph. M.
	and their assistants

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**Volatilization of Mercury from Wrapped Powders of Mercury with Chalk.** I. Roberts. *Pharm. J.* 86, 487 (1938). Samples of wrapped one grain powders of Grey Powder have been bought in which it was found that all the mercury had been lost through the volatilization of mercury on long storage. In the investigation herein reported a study was made of the rate of such loss under different methods of storage and packaging. When stored in tightly stoppered bottles Grey Powder shows little or no loss of mercury. In the case of powders enclosed in a powder box the outside powders show much greater loss than those in the center of the pack. Most interesting of all was the difference in the amount of loss depending upon whether a rough cardboard or glazed cardboard box was used as a container, the rough cardboard box permitting a drop in the outside powders from 32.9 per cent. Hg to 10.9 per cent. in eight months as compared with 32.9 per cent. to 30.2 per cent. in the case of similar powders packaged in glazed cardboard.

High temperatures of storage was found to very greatly increase the loss of mercury and consequently preparations containing Grey Powder should be stored in a cool place. L. F. T.

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**Antiseptic and Bactericidal Action of Benzoic Acid and Inorganic Salts. Effect of pH.** R. H. Goshorn, Ed. F. Degering and P. A. Tetrault. *J. Ind. Eng. Chem.* 30, 646-8 (1938). The maximum dilutions at which benzoic acid solutions will function effectively as a bactericide and as a bacteriostatic agent were determined at various pH values using *Bacterium coli* and *Staphylococcus aureus* as test organisms. Benzoic acid was found to be non-effective as a



bactericidal or bacteriostatic agent in the neutral range. The pH at which the dilution-pH curve breaks is, for both organisms, approximately 4.4 for bactericidal action and an average of 6.1 for bacteriostatic action. Sodium benzoate was found to be relatively ineffective in neutral or alkaline solution, but decidedly effective when converted to the free acid by the acidity of the media.

Solutions of calcium, potassium, and sodium chloride, and of sodium nitrate and sulfate are not effective as bacteriostatic agents except at rather concentrated solutions at a pH of 5 or 6. Sodium chloride is effective in about one-half the concentration at a pH of 5 as it is at a pH of 6. The other salts tested gave similar results.

G. W. P.

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**Autoxidation of Terpenes in Petroleum Solvent.** J. N. Borglin. *J. Ind. Eng. Chem.* 30, 639 (1938). Petroleum-terpene hydrocarbon blends, obtained in the steam and solvent process for extracting wood rosin from southern pine stumps, contain in excess of 50 per cent. terpene hydrocarbons, of which pinene is the major constituent. Mixtures of this type on long storage oxidize and precipitate. There is an induction period of about three months after which oxidation was found to be rapid and uniform.

Tricresyl phosphate,  $\alpha$ -terpineol, aluminum flake, dry sodium carbonate, dry calcium oxide and dry zinc oxide accelerated autoxidation. Borax and trisodium phosphate, dry or moist, had no effect. Sodium hydrosulfite (moist or dry), aqueous ammonia, anethole, moist sodium carbonate, moist calcium oxide, triethanolamine, methanol and ethanol were found to be effective in retarding autoxidation. Ethanol is more effective than methanol. The tests were carried out over a period of ten months using concentrations of 1 per cent., of the materials noted above.

G. W. P.

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**Color Change Caused by Deuterium,** *Science News*, 87, No. 2263 (1938). The first recorded case in which the substitution of heavy hydrogen, or deuterium, for ordinary hydrogen in a chemical reaction produces a color change, is reported in the *Journal of Chemical Physics*. Professor Victor K. LaMer and Samuel H. Maron, of Columbia University, describe their color-change experiments which are still in progress. It is well known that the substitution of a deuterium atom (D) for a hydrogen atom (H) in chemical compounds produces a material with different physical characteris-

tics but, until the LaMer-Marion experiments, this change was never observable to the senses. In the tests the change from hydrogen to deuterium atoms produced a light yellow color in a previously clear solution. The chemicals involved in the tests were a solution of proto-nitroethane in heavy water and a compound made of barium, oxygen and deuterium.

L. J. K.

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**Estimation of Ascorbic Acid in Citrus Juices.** J. W. Stevens. *Ind. and Eng. Chem. Anal. Ed.*, 10, 269-271 (1938). Certain improvements in the standard iodine titration method for the determination of ascorbic acid have been proposed. It is claimed that these modifications increase the specificity of the method for Vitamin C and also improve the sharpness of the end point. Detailed directions for preparation, standardization, and storage of the solutions employed are included. The procedure for the actual determination set forth in this article differs from the ordinary iodine method in two respects: the high acidity (a pH of 0.02 to 0.08) and the double back-titration. Less acid media lead to a sluggish end point. The titration is carried out by adding first an excess of iodine, then an excess of thiosulfate, finally completing the titration with iodine. The end point is easier to recognize when carried out in this manner. Results obtained by this method compare favorably with those obtained using other methods.

L. A. R.

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**Determination of Formic Acid.** J. D. Reid and H. D. Weihe. *Ind. and Eng. Chem., Anal. Ed.*, 10, 271-272 (1938). A method and apparatus for the determination of formic acid, in the presence of several other organic acids and alcohols, is described. The method utilizes a solution of mercuric acetate as an oxidizing agent, oxidizing the formic acid to carbon dioxide. The carbon dioxide is then absorbed in a fritted-glass absorber using tenth-normal sodium hydroxide solution. The sodium carbonate thus formed is precipitated as barium carbonate, and the excess alkali determined by titration with acid. A blank is run under identical conditions. Experimental data show the method to be accurate within an average error of 0.4 per cent.

L. A. R.

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**A New Process for Color Photography.** *Science News*, 87, No. 2263 (1938). A new color photographic process that would use a layer of differently dyed red blood corpuscles as filters for

separating colors in order to record them on film has been patented by Chalmers C. Smith, of Glendale, Calif., and Roy H. Pinker, of Los Angeles.

Use of the corpuscles, the inventors claim, represents an advance over present color photography technique, which uses either a ruled screen or a layer of starch grains to achieve the color separation. Colored motion pictures and still photographs are all made essentially by using one or another means to separate the three primary colors that make up all shades and tints and to record them separately, then put them together again for viewing purposes. Practical development of the process might well mean a fundamental change in the technique of making colored motion pictures used at present. These are made by means of a triple-coated film, one layer with its associated filter being sensitive to one of the primary colors. This process has, however, serious practical limitations. The screen processes are not used in commercial color motion pictures because the starch grains and the rulings show in the enlargements thrown on the screen.

The red blood cells of sheep, 0.003 millimeter across, are sufficiently small so that when enlarged 240 diameters in being thrown on a screen as in motion picture projection, they would still be less than a millimeter in diameter, a size small enough perhaps not to show. A further advantage claimed for the idea of using a corpuscle screen is that the corpuscles are more translucent than starch grains, cutting down the amount of light required for taking pictures, and are also more regular.

L. J. K.

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**A New Synthetic Flyspray Base.** *Ind. & Eng. Chem. News Ed.* A new synthetic flyspray base capable of replacing a substantial proportion of the pyrethrins now used in household insecticides has been announced by E. I. du Pont de Nemours & Co. The compound is isobutyl undecylenamide, the result of an intensive investigation because of the increasing difficulty of getting a uniform and reliable source of pyrethrum for the extensive flyspray market.

Attempts to cultivate pyrethrum in the United States have been unsuccessful because this country cannot compete with cheap foreign labor in harvesting the flower heads. The crop varies widely from year to year in both quality and quantity. There is little authentic information available until after the harvest and American importers must buy it sight unseen. The present Sino-Japanese conflict has

caused even more uncertainty. Isobutyl undecylenamide as an ingredient for flyspray not only has proved extremely efficacious but it has also been shown by careful toxicological study to be non-injurious when so used on humans or household pets. L. F. T.

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**The Behavior of Solutions of Soaps and Wetting Agents Toward Semi-Permeable Membranes.** H. Kröper. *Dermatol. Wochschr.* 106, 381 (1938) through *Squibb Abstr. Bull.* 11, 900 (1938). The dialyzability through cellophane of solutions of K soaps of lauric, myristic, palmitic, stearic, oleic, linoleic, ricinoleic acids and the dialyzability of solutions of fatty alcohol sulfates (Cyclanon L and O) and of fatty acid condensation products (Igepon 702K, KT, T, and AP) were found to vary directly with the wetting and cleansing power of these substances and their irritating power. The theory that irritation by soaps is due to free alkali released by hydrolysis is contradicted by the fact that the most irritating soaps i. e., those of lauric and myristic acids are least hydrolyzed while the least irritating soaps i. e., those of stearic, palmitic, and oleic acids are the most hydrolyzed. L. F. T.

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**The Toxicology of the Narcotic Drugs.** G. R. Lynch. An Address. *The Analyst*, 63, 240 (1938). Attention is drawn to this most excellent and informative presentation relative to the toxicology of numerous narcotic drugs. The barbiturate group is given particular emphasis and the article points out many important facts which illustrate clearly the author's wide experience in this field. Over 100 cases of barbiturate poisoning represent the basis for the toxicological findings reported, and a tabular comparison is made of the different clinical findings made in cases wherein eleven different barbiturate drugs were the cause of poisoning. Chemists engaged in this field should not miss reading this address in full. L. F. T.

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**The Preservative Properties of Ethylene and Propylene Glycol.** J. Rae. *Pharm. J.* 86, 517 (1938). A study of the preservative action of ethylene and propylene glycol on a series of different solutions subject to bacterial or mold growth was made in order to evaluate these substances as preservatives. The solutions employed were aqueous tannic acid, diluted syrup, a gelatin solution, and tragacanth jelly.

The summarized results were as follows:

*Tannic Acid*—Both glycols were superior to glycerin and alcohol since alcohol (10 per cent.) although it preserved the solution did not prevent the formation of a deposit on standing as did 10 per cent. propylene glycol or 20 per cent. ethylene glycol.

*Syrup*—Both glycols in the lowest percentage tried, namely 10 per cent., were effective in preventing mold growth as was alcohol. Glycerin in 10 per cent. concentration was not effective but 20 per cent. was.

*Gelatin*—Ethylene glycol was effective in concentration of 30 per cent. Propylene glycol in concentration of 20 per cent. was effective but caused some precipitation of gelatin. Ten per cent. alcohol was quite effective but even 40 per cent. glycerin failed to prevent growth.

*Tragacanth*—Ten per cent. alcohol, ethylene or propylene glycol were all satisfactory but even 40 per cent. glycerin was not effective.

L. F. T.

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**The Sterilization of Sodium Bicarbonate Solution for Intravenous Use in Acidosis.** F. E. Holmes and G. E. Cullen. *J. Lab. Clin. Med.* 23, 761 (1938) through *Squibb Abstr. Bull.* 11, 849 (1938). Sodium bicarbonate solutions may be sterilized without alteration to the more alkaline normal carbonate by the following simple technic. Five per cent. solutions are prepared using a pure sodium bicarbonate and freshly distilled water. Phenolsulfonphthalein is added as an indicator and the solution is filtered through a Berkfeld filter. One hundred cc. portions of this solution are placed in 125 cc. pyrex bottles and then CO<sub>2</sub> is bubbled into the solution until the color is a yellowish peach and the solution saturated with CO<sub>2</sub>. The bottles are immediately stoppered with vaccine stoppers having a retractable flap, the bottles are placed in a clamp and autoclaved. After autoclaving they are allowed to cool before removing the clamp and afterwards they are shaken to redissolve the CO<sub>2</sub> which has been driven off. Any pink color less than a deep purplish red indicates that there has been no loss of CO<sub>2</sub> from the bottle and that the pH is between 7.0 and 8.0. When relatively large batches are prepared for hospital use it is convenient to filter through a Berkfeld "N" filter and to use a tube with a sintered glass tip for the aeration in order to facilitate more rapid absorption of CO<sub>2</sub>.

L. F. T.

## SULFANILAMIDE AND RELATED COMPOUNDS (A BRIEF REVIEW AND BIBLIOGRAPHY)

By Louis Gershenfeld, Ph. M., B. Sc., P. D.

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Chemotherapy has shown marked progress during the past year especially due to the numerous reports on the action of sulfanilamide. The author presented various data during 1937 concerning these compounds in the January and July issues of this JOURNAL. Since this last report the Council of Pharmacy and Chemistry of the American Medical Association accepted sulfanilamide for admission to New and Non-Official Remedies. (*J. Am. Med. Assoc.*, 109, 358 (1937)). They report the oral dose as 1 gram (15 grains) for each 20 pounds body weight up to 100 pounds. Five grams is the maximum daily dose which has been used with safety in adults of average weight, this being divided into four doses given six hours apart. Smaller doses of 3-4 grams daily have been found sufficient. Intraspinal and intravenous administration are still experimental. Further comments by the Council on the bactericidal action of sulfanilamide are reported. (*J. Am. Med. Assoc.*, 109, 1454 (1937)).

An exceedingly large number of papers have been published reporting the action of sulfanilamide and related compounds on almost all kinds of bacterial diseases. Much favorable comment is recorded on their use in infections caused by the streptococcus, gonococcus, and meningococcus. Type III pneumococcus infections responded very favorably to these compounds. Reports were also presented revealing experiences with these drugs in staphylococcus infections and in the following abnormalities: Mastoiditis, otitis media, sinusitis, bacterial endocarditis, rheumatic fever, undulant fever, in experimental poliomyelitis and other virus infections, in malaria, gas gangrene, gangrene ballanitis, B. coli infections, pyelitis, cystitis, and other urinary infections and bovine mastitis. Interesting reports were also recently presented on a para-typhoid B, and a streptococcus carrier successfully treated with sulfanilamide.

Considerable data has also been presented in which symptoms of sulfanilamide intoxication are described, in detail. Complications following the use of these compounds and various idiosyncrasies have been reported. Dermatitis and skin eruptions and rashes have been recognized as possible aftermaths. Cyanosis, hemolytic anemia,



methemoglobinemia, sulfhemoglobinemia, agranulocytosis and other objectional reactions have been recorded. Numerous workers caution against the indiscriminate use of these products. In this connection comments by Grabfield (*New Engl. J. Med.* 216, 911 (1938)) are of interest. In his paper on "The Relation of Newer Drugs to the Public Health," he says, "The health officer is advised to preach constantly of the evils and dangers of self-medication and of the improper use of good drugs by physicians. New remedies introduced by substandard pharmaceutical houses should be carefully scrutinized and distribution by the State of certain important drugs should be carefully studied, 'if only as a threat to check the exploitation of the lay and medical public by unscrupulous manufacturers'."

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## SOLID EXTRACTS

By Ivor Griffith, Ph. M., Sc. D.

Despite the form in which this information is presented it may be accepted as trustworthy and up-to-date. Original sources are not listed but they may be obtained upon request.

"The veil between the two worlds is but a sheer cloud and one passes through it imperceptibly." Yet actually, death is a most progressive action. One literally dies by inches.

After an individual has ceased to breathe, and his heart has stopped, his organs and cells continue to live.

The brain and liver die first.

The heart follows the brain and liver in death. A stopped heart can be restarted several times with adrenalin injections, electric needles or manipulation by hand.

Remaining parts of the body die in this order: big muscles, stomach and intestines, cartilage and bone, and finally the skin.

There is an erroneous idea that fingernails and hair grow after death. What actually happens is that flesh, receding from the nail and hair, discloses nail and hair tissue which had already grown before death.

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*According to a Philadelphia metallurgist three-quarters of the so-called less familiar elements were discovered a century or more ago, and yet their industrial applications began only within the last twenty-five years. This belated recognition can be attributed to inadequate methods of recovery and refining, the popular belief that the ores of many of them were available in only very limited tonnages, and the failure to correlate laboratory studies with industrial needs.*

*It is probable that within the next fifty years many of the well-known metals may become outmoded in favor of the relatively more abundant but less known metals of today. Zirconium, for example, is more abundant than nickel, vanadium, or copper.*

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Saffron, primarily valued as a dye, was also used medicinally until long after the end of the Middle Ages. As late as in the eighteenth

century, Theodore Zwinger (1658-1724), Professor of Anatomy and Botany at Basle, gave it unstinted praise as a medicine. Among Zwinger's numerous writings "Der Sichere und Geschwinde Arzt" (The Safe and Speedy Physician), which ran into five editions, was the most popular. Its author was showered with titles and dignities by foreign princes and learned societies, and the medical schools of Leyden, Berlin, and Cassel, attempted in vain to lure him from Basle.

In his "Theatrum Botanicum" this notable scholar praises the exceedingly "fine virtues" of saffron. It soothes pain, strengthens liver, heart, spleen, and uterus, clears the respiratory channels, and eases breathing. But Zwinger recommends it most warmly as a remedy against colic in infants.

"If infants are perpetually screaming and will not drink, that is a sign that they have gripes in the belly, and should be given a small quantity of powdered saffron with their milk." However, he warns against too liberal use of saffron both for children and adults, as it is apt to produce such joy of mind that there is grave risk the patient will laugh himself to death!

But one of the most quaint uses of saffron, and on the most ardent recommendation is, in a weak infusion, as restorative for tired homing pigeons, upon return from a long airjaunt.

*That our calendar is incorrect is now an accepted fact and instead of being 1938 this year is actually 1931, since from the point of view of religious history, language and astronomy Christ was born in what we improperly call 7 B. C.*

*There are three essential facts which help us to ascertain the year when Christ was born: the first enrolment decreed by Augustus (St. Luke 2), the death of Herod (St. Matth. 2, 19), and the Star of the Wise Men from the East (St. Matth. 2). It has been proved by authentic sources discovered in our time that a census taking place every fourteen years was introduced under Augustus, that, according to the regulations of this census, Joseph had to travel to Bethlehem with Mary, in order to be "enrolled" (St. Luke, 2, 4f), and that in Syria a census took place, when Quirinius, who is mentioned in St. Luke 2, 2, was officiating in that district. To judge from the dated documents, that census began in 10/9 B. C. The fact that Herod died in 4*



*B. C. was inferred without any doubt from numerous statements on the part of Josephus and Dio Cassius, which are confirmed by coins. Thus Jesus was born between 9 and 5 before our Christian Era.*

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The word kermes is of Oriental origin. It means worm; the Sanscrit form is krmi, in ancient Iranian it is known as kerema and in Lithuanian as kirmis. The Arabs describe it as Dûd il Quïrmis. The Bible, which furnishes the oldest evidence of the existence of this dye, uses the Hebrew name tola or tolaat, also meaning worm, and generally used in conjunction with the word schani, bright red, so that the name might be rendered as scarlet worm.

The word kermes has found its way into nearly every European language. Crimson, cramoisi (French) and Karmin (German), are all derived from the same root. During the Middle Ages the name vermilium (small worm) came into use, hence vermilion and the French vermeil.

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*When, in 1512, the Spaniards landed in Mexico they became acquainted with a red dye, which was used by the natives both for dyeing and painting. In the language of the Aztecs this dye was called "Nochezli". The Spaniards, who at once recognized its resemblance to their native kermes, called the new dye grana cochinilla. Cochinilla is a diminutive derived from the Latin word "coccinus" = scarlet-colored. The word cochineal, current in English, is an Anglicized form of the same word, and of a kindred origin is the Welsh word coch meaning red. Color names in that language carry a really significant history. Llwyd, or grey, gives rise to Mr. Lloyd; blue is glâs (glacé), white is gwyn, black is du (Roderick Ddu), yellow is melyn, perhaps allied to the pigment word melanin, etc.*

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Clay or earth-eating, known to word-heavyweights as geophagy, is not a practice confined to savages, but occurs sporadically in all sections of earth.

In India, where the habit perhaps is more widely spread than in any other country and where it has developed into a veritable passion with many individuals, especially women, the appalling effects have grown proportionately. Here again, however, experiences recorded as to ill effects of clay-eating vary a great deal. One observer in India who made wide inquiries from women habitually eating clay

was invariably informed that they experienced no ill effect whatever. Another correspondent who has known numerous instances of earth-addicts in Mysore reports that "the habit once contracted by women is rarely, if ever, abandoned by them, and is invariably followed by fatal results."

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*The United States with only 7 per cent of the world's population, consumes 48 per cent. of the world's supply of coffee; 53 per cent. of the world's supply of tin; 56 per cent. of the world's supply of rubber; 21 per cent. of the world's supply of sugar; 72 per cent. of the world's supply of silk; 36 per cent. of the world's supply of coal; 42 per cent. of the world's supply of pig-iron; 47 per cent. of the world's supply of copper; 69 per cent. of its crude petroleum.*

*And to boot, we make and own 70 per cent. of the world's automobiles, and control practically the same percentage of its telephones and telegraphs.—But still we have the recession!*

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### Glass Marking Ink with Simple Glycerine Formula

When an ink-marking on glass is desired, an effective ink for this purpose is easily made with the following formula:

Glycerine .....	40
Barium sulfate .....	15
Ammonium bifluoride .....	15
Ammonium sulfate .....	10
Oxalic acid .....	8
Water .....	12

All parts by weight. The viscosity may be adjusted with water. Use the mixture in a hood or a well-ventilated room. To speed the action, up to 5 per cent. of sodium fluoride may be added.

Glycerine is extensively used in the manufacture of practically all types of inks because of its solvent properties and its unique power of absorbing and retaining moisture.

## BOOK REVIEWS

Done by persons, unafraid to upbraid, but perfectly willing to give praise where praise is really due.

STARZENSTEIN'S TEXTBOOK OF PHARMACOLOGY, TOXICOLOGY AND PRESCRIPTION WRITING. 758 pages 40 illustrations. Deuticke, Leipzig, 1938, unbound, price 20 marks in German.

According to the author, the marked success of those phases of medical science dealing with medicinal therapy, due to exact pharmacological research, has clearly emphasized the value of pharmacology as its foundation. This fact assures pharmacology a place in teaching and research, which, he feels, it will always occupy in medicine and medical art.

He urges the student to enhance the understanding of the systematic, theoretical instruction with the varied experience obtainable at the sickbed, and, may the reviewer add, with the observations made upon experimental animals. All biological workers will agree with the author's admonition to students, "One look into the book, two into life."

The subject matter is interestingly discussed in chapters dealing with general pharmacology, toxicology and special pharmacology. The author describes with gratifying clarity the function of body organs, life processes, and substances affecting them. While the reviewer regrets with the author that the bibliography had to be omitted from this text book for sake of brevity, he believes that the student should become familiar at least with the creative workers in important fields of research. There are practically no authors mentioned in the field of vitamin research and very few in that of hormone and gland research. The latest accomplishments of pioneers and foremost biochemists should be known to students of pharmacology as the personal achievements of certain leaders and their schools.

These remarks are made particularly with the hope that the book may prove popular with the student and that then the names, as well as the work of the masters may be found in the revision.

A. VIEHOEVER.

QUALITATIVE ANALYSIS FOR STUDENTS OF PHARMACY AND MEDICINE. Charles B. Jordan, Ph. C., M. S., D. Sc. and Henry George DeKay, Ph. D. McGraw-Hill Book Company, Inc., 330 West Forty-second Street, New York, N. Y., 1938. 178 pages. Price: \$2.50.

The book is divided into three parts consisting of, first, a theoretical introduction of 36 pages; second, an 85-page section dealing with metal analysis; third, a 44-page discussion of the detection of anions, the complete systematic analysis, the preparation of salt and test solutions together with a table of solubilities.

In accordance with one of their stated objectives, the authors call attention to many "medical-pharmaceutical applications" of qualitative analysis. Another objective is to introduce a work modern in theory; toward this end the authors discuss or mention the more important theoretical concepts, but, in the opinion of the reviewer, oftentimes weaken their presentation by selecting poor examples to illustrate the various points. Thus, in the discussion of solubility product, sodium chloride—a salt to which the solubility product principle does not apply—is used as the example. Similarly inappropriate systems of strong electrolytes are used as examples in discussing chemical equilibrium and the law of mass action.

Despite these weaknesses the book contains much valuable information presented in a concise form suitable for the use intended.

ARTHUR OSOL.